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10/078,757	02/19/2002	Carlos F. Barbas III	TSRI 598.0 Con.1	7970

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/078,757	BARBAS ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-15 are pending and under examination.

Specification

2. The disclosure is objected to because of the following informalities:

The first line of the specification needs to be updated to indicate application 08/986,016 is abandoned.

Appropriate correction is required.

Claim Objections

3. Claim 6 is objected to because of the following informalities: The claim should ad the term "a" after "to" and before "whole antibody". Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-4 are indefinite for reciting "in which each chain" in line 4 of claim 1 because it is unclear how each chain can have at least one CDR when only one chain is constructed.

b. Claims 1-4 are indefinite for reciting "in which each complementarity determining region (CDR) loop" in part (b) because it is unclear if 1 or 2 or all 3 CDRs are included.

c. Claim 1 part (b) recites the limitation "said second library" and "said first library chains in the claim. There is insufficient antecedent basis for this limitation in the claim.

d. Claims 5-15 are indefinite for reciting incomplete method claims which do not include a resolution step which reads back on the preamble of the claimed method. Merely "selecting from the humanized pair library a particular humanized pair heavy and light chain for binding to said selected antigen" does not result in a method of producing a humanized mouse monoclonal antibody. The claims should conclude with a step of producing the antibody as required by the preamble, which recites "a method of humanizing a mouse monoclonal antibody heavy and light chain pair".

e. Claim 1 part (c) recites the limitation "said library" in step (a). There is insufficient antecedent basis for this limitation in the claim.

f. Claims 2-3 are indefinite for reciting that the human library contains light chains and the complementary chain is a heavy chain or visa versa because it is unclear which library is claimed because claim 1 requires both a heavy and light chain.

g. Claims 5-15 are indefinite for reciting "said light chain" in part 5(a) because it is unclear if you mean the human light chain or not.

h. Claims 5-15 are indefinite for reciting "said heavy chain" in claim 5(c) because it is unclear if the heavy chain is the one being constructed or the one in part (b).

i. Claims 9-10, 12-13 are indefinite for reciting "wherein only a light chain CDR3 from the mouse antibody is grafted onto the human light chain in place of the human light chain CDR3" (claim 9, for example). From this language it is not clear whether only one of the CDRs are grafted or whether additional, non-CDR residues may also be grafted onto the human light chain variable region. In addition, it is not clear if only CDR is grafted into all of the CDRs. Additionally, in claims 12-13, it appears that the human light chain or heavy chain not only contains a single CDR and lacks not only any human framework regions residues but also lacks the other two CDRs, albeit human or mouse in origin. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 12-13 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does

not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

This rejection is made because it is unclear if the LM609 antibody in the specification is the same as that recited in the claims. It is unclear if a cell line which produces an antibody having the exact chemical identity of HB 9537 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the

claimed antibody species HB 9537. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-11, 14, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoogenbloom et al (US Patent No: 5,565,332) in view of Adair et al (US Patent 5,859,205).

The claims are drawn to a method of humanizing mouse antibodies by constructing a libraries of human light chains containing at least one mouse CDR, combining the libraries with a complementary heavy chain, and selecting the humanized pair using another complementary antibody chain that binds a pre-selected antigen. A heavy chain can comprise an Fd fragment that is either chimeric mouse/human heavy

chain fragment or a template mouse heavy chain fragment. The library can consist of human/mouse chimeras in which the only mouse component is a mouse CDR3 sequence. Finally, the method can include the additional step of converting a heavy chain-light chain pair into a whole antibody.

Hoogenbloom et al teach a general method of humanizing antibodies by using phage display libraries. A repertoire of either light chains or heavy chains comprising at least the light chain or heavy chain variable region is created and combined with a complementary heavy or light chain to form a Fab fragment. The process is then repeated by creating libraries of heavy chains or light chains to form a fully humanized Fab fragment (column 24, lines 1-44 and Figure 1). Hoogenbloom et al teach that both light chain and heavy chain libraries may be generated. Hoogenbloom et al further teach that the heavy chain may be a mouse/human chimera Fd fragment (column 24, lines 45-46), or may be a template mouse heavy chain fragment (encompassed by claim 19). In addition, Hoogenbloom et al teach that the method can be combined with CDR-imprinting methods to create a human light or heavy chain library containing a mouse CDR3 sequence (Abstract, column 9 lines 4 through 8, column 30 lines 15 through 49, and column 35 line 44 through 65). Finally, Hoogenbloom et al teach making human antibodies from phage libraries (column 41, lines 63-67). Hoogenbloom et al teach that the methods may be combined with CDR-imprinting (Abstract, lines 15-16), and that CDR imprinting is synonymous with CDR-grafting (column 1, lines 31-32). Hoogenbloom et al further teach that humanization of monoclonal antibodies can be of great value in therapy and diagnosis (column 3, lines 8-10). In addition,

Hoogenbloom et al state that the provided working examples are intended to illustrate the invention without limitation (column 14, lines 3-4). While the reference teaches that the methods may be combined with CDR grafting, the reference differs from the instant invention by not specifically teaching that mouse CDRs may be grafted onto the light chain or heavy chain of human variable domains.

Adair et al teach a general method of grafting mouse CDR onto human framework regions. Adair et al teach that his can be accomplished for both heavy and light chains. Specifically, Adair et al teach that mouse CDR can be grafted onto human framework regions (column 26, lines 55 through 65). Adair et al provide motivation for humanizing antibodies for diagnostic or therapeutic purposes (see Abstract) as it would be highly desirable to diminish or abolish this undesirable HAMA response (col 1, line 67 to col 2, line 1). Adair teaches in Fig 5 and 6 and Table 2 that CDR3 of either the light or heavy chain may be flanked with unaltered human framework regions 3 and 4.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the phage display method taught by Hoogenbloom et al with the method of grafting mouse CDR onto human light chain framework regions taught by Adair et al in order to make humanized antibodies.

One of ordinary skill in the art at the time the invention was made would have been motivated to and had a reasonable expectation of success to have incorporate the grafting method to a murine CDR into a human light chain as part of the general phage display method (1) because Hoogenbloom et al explicitly teach that the phage display methods can be combined with CDR grafting and (2) because Adair teach the

importance of diminishing or abolishing the undesired HAMA response by CDR grafting methods. Referring to the phage display methods in general implicitly suggests that murine CDR can be grafted onto one or both of the human framework regions. While the preferred embodiment disclosed in columns 8 and 9 of Hoogenbloom teaches only grafting a CDR to a heavy chain, this does not teach against the explicit suggestion that the methods (plural) can be combined with CDR-imprinting found in the Abstract. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because of the success Adair et al had in producing humanized antibodies and in view of the explicit teachings of Hoogenbloom to combine the methods.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

10. Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoogenbloom et al (US Patent No. 5,565,332) in view of Adair et al (US Patent 5,565,332) and Brooks et al (The Journal of Clinical Investigation, Vol. 96, pages 1815-1822 (1995)).

The claims are drawn to a method of humanizing mouse monoclonal antibodies by constructing phage display library of the light chains comprising at least CDR3 from the mouse antibody LM609, selecting one of the chains using a heavy chain, and

repeating the process using a heavy chain library. Alternatively, the heavy chain can comprise at least CDR3 from the LM609 antibody.

Hoogenbloom et al and Adair et al are discussed supra. The references differs from the instant invention by not specifically disclosing humanizing the LM609 antibody using phage display libraries.

Brooks et al teach that administration of LM609 either prevented tumor growth or markedly reduced tumor proliferation (Abstract). Brooks et al further teach that administration of the LM609 antibody may offer an effective treatment for human breast cancer and tumor angiogenesis (page 1820, second paragraph).

It would have been prima facie obvious for one of ordinary skill in the art at the time the claimed invention was made to use the phage display library method taught by Hoogenbloom et al to humanize the LM609 antibodies used as a tumor therapy taught by Brooks et al.

One of ordinary skill in the art would have been motivated to use the LM609 antibody in the phage display humanization method of Hoogenbloom et al and Adair et al because (1) Hoogenbloom et al teach the therapeutic usefulness of humanizing antibodies, because (2) Adair teach the importance of diminishing or abolishing the undesired HAMA response by CDR grafting methods and because (3) Brooks et al clearly teach the use of LM609 antibodies as a potential cancer therapy. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because of the success Hoogenbloom et al and Adair had in their methods and

because once a murine antibody is isolated with desirable binding properties, grafting of the CDRs onto human framework regions is successful in reducing the degree of HAMA response upon administering the antibody to a human patient for diagnosis or treatment methods.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 703-872-9306.

LARRY R. HELMS, PH.D
PRIMARY EXAMINER